

Remarks

Amendments

Claims 37, 39, 43, and 91 are amended to eliminate one of two alternatives. Rather than “one or more,” the claims are amended to recite “more than one.” This amendment adds no new matter.

Each independent claim is amended to clarify the intended meaning. “Microemulsions” is used as a collective term referring to a collection of aqueous compartments in an oil phase. “Aqueous compartments” refer to the individual compartments or bubbles within the collective.

New dependent claims 99-105 are presented. These recite particular samples, such as bodily fluids or tissue of a eukaryotic organism. These are supported at page 12, paragraph 36 of the specification.

The rejection of claims 37, 43, 45, 60, 91, 92, and 95-98 under 35 U.S.C. § 103(a)

Claims 37, 43, 45, 60, 91, 92, and 95-98 stand rejected as unpatentable over Holliger in view of Vogelstein and Paulsen. This rejection is respectfully traversed.

As amended, each of the independent claims in the rejected claim set, *i.e.*, claims 37, 43, 45, 60, and 91, recites that the microemulsions comprise *more than one* species of analyte DNA molecules. Each of these claims subsequently recites that product beads are formed that are bound to a plurality of copies of a *single* species of analyte DNA molecule. (See specification at page 8, paragraph 27, and page 9, paragraph 28.)

Holliger is cited for its teaching in Example 25 (the first example 25), in which individual *cells* are distributed in compartments with PCR reagents and a bead. Upon amplification within the compartment, PCR fragments from one single cell are transferred to a bead. Holliger does not teach, however, a method to obtain from a single cell which comprises more than one species of analyte DNA a product bead that is bound to a plurality of copies of just one species of analyte DNA molecule. Either Holliger was contemplating use of prokaryotic cells comprising a single chromosome (*i.e.*, one species of analyte), or Holliger was not interested in separating two distinct species of an analyte. In either case, Holliger does not teach a method to convert more than one species of analyte DNA molecule in a single compartment to just one species of analyte DNA molecule on a bead. This would be necessary were one to use Holliger's teaching and distribute cells to compartments.

Thus, contrary to the assertion of the Office Action that if only one biotinylated primer were used, then each bead would be bound to a plurality of copies of one species of analyte DNA molecule, this would not be true if the starting materials in the compartment contained more than one species of analyte DNA molecule. Thus Holliger does not teach the method of independent claims 37, 43, 45, 60, and 91.

The secondary references are cited as teaching additional limitations that are found in various claims as subsequent steps, such as using differentially labeled oligonucleotide probes, using probes with a stem and loop structure, determining a proportion of variant sequences within a DNA sample, amplifying onto magnetic particles, using biotin-streptavidin to bind primers to beads, and sorting beads. Whether or not these assertions are true, Holliger did not teach a means of starting with a mixed or heterozygous population of analyte species, *i.e.*,

comprising more than one species of analyte, and make beads that are homozygous for one species of analyte species. The secondary references do not teach a way to modify Holliger's teaching to form the method that is the subject of the rejected claims. Thus the *prima facie* case of obviousness fails.

Please withdraw the rejection.

The rejection of claims 91 and 93 under 35 U.S.C. § 103(a)

Claims 91 and 93 stand rejected over a combination of Holliger, Paulsen, and Cohen. Claims 91 and 93 specifically recite use of allele specific priming to determine a sequence feature of the one species of analyte bound to a bead. Neither Cohen nor Paulsen remedies the defect in Holliger's teaching: Holliger does not teach how one would start with microemulsions comprising more than one species of analyte DNA molecule and make beads that are bound to just one species of analyte DNA molecule. Paulsen is cited for teaching magnetic beads attached to primers and removal of strands not bound to the beads. Cohen is cited as teaching allele specific priming. Neither Paulsen nor Cohen remedy the defect in Holliger. Therefore the combination of references fails to make a *prima facie* case of obviousness.

Please withdraw this rejection.

The rejection of claims 91 and 94 under 35 U.S.C. § 103(a)

Claims 91 and 94 stand rejected over Holliger, Paulsen, and Nikiforov. These claims are directed to a step of determining a sequence feature using a single nucleotide extension reaction, after forming homogeneous beads from a heterogeneous population of analyte species. The

starting material contains more than one species of analyte and resultant beads contain a single species of analyte DNA molecule.

Holliger and Paulsen have been discussed above. Nikiforov is cited as teaching use of single nucleotide extension reaction to determine a sequence feature. Whether or not it is true that it would have been obvious to make the combination of teachings asserted, none of the secondary references remedy the defect of the primary reference, Holliger. Thus a *prima facie* case has not been made.

Please withdraw this rejection.

The rejection of claims 39 and 62 under 35 U.S.C. § 103(a)

Claims 39 and 62 stand rejected as obvious over Holliger, Paulsen, and Chang. Each of the rejected claims recites isolating product beads which are bound to a plurality of copies of one species of analyte DNA and amplifying that one species. Chang is cited as teaching the use of amplification for generating large amounts of DNA for sequencing and analyzing mutations. Chang does not, however, remedy the deficiency of Holliger or of Holliger combined with Paulsen. None of the references teaches a way to capture a single species of analyte on a bead from a mixed population comprising more than a single species of analyte DNA.

Please withdraw this rejection as well.

Applicants request that this application again be processed for grant.

Cross-reference

Applicants remind the examiner of the co-pending child application 12/361,690.

Applicants invite the examiner to review the issues raised in the child application for appropriateness to the subject claims. Applicants invite the examiner to consider any other issues that may arise with a child application, including but not limited to double patenting.

Respectfully submitted,

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